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α_1-Adrenoceptor-mediated sympathetically dependent mechanical hyperalgesia in the rat

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Abstract

The model of rolipram (a type IV phosphodiesterase inhibitor) induced prolongation (> 3 days) of the mechanical hyperalgesia produced by the intradermal injection of prostaglandin E_2 in the hairy skin of the hindpaw of the rat, measured by the Randall-Selitto paw-withdrawal test, was employed to study mechanisms involved in the contribution of the sympathetic postganglionic neuron to mechanical hyperalgesia. Lumbar surgical sympathectomy prevented rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Decentralization of sympathetic postganglionic neurons innervating the hindpaw did not, however, effect rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Phentolamine, an α-adrenoceptor antagonist, and prazosin, an α_1-selective adrenoceptor antagonist, when given systemically or intradermally at the site of injection of prostaglandin E_2 and rolipram, blocked rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Intrathecal administration of phentolamine and prazosin were, however, without effect on rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Yohimbine, an α_2-adrenoceptor antagonist given systemically, intradermally or intrathecally also did not produce any alteration in rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. We propose that sympathetic postganglionic neurons are involved in rolipram-induced prolongation of prostaglandin E_2 hyperalgesia and that this form of sympathetically dependent hyperalgesia, which is independent of activity in preganglionic sympathetic neurons, is mediated by a peripheral α_1-adrenergic mechanism.

Keywords: Hyperalgesia; Prostaglandin E_2; Phosphodiesterase; Rolipram; Sympathetically maintained pain

1. Introduction

While the sympathetic postganglionic neuron has been shown to contribute to sensory abnormalities in a variety of pain states in humans (Arner, 1991; Raja et al., 1991; Treede et al., 1992; Wahren et al., 1991) and in animal models (Kim and Chung, 1991; Neil et al., 1991; Shir and Seltzer, 1991; Xie and Xiao, 1990) the mechanism of the sensory-sympathetic interaction is still poorly understood. We have recently described a novel model of sympathetically dependent mechanical hyperalgesia (Aley et al., 1994) which involves prolongation of the mechanical hyperalgesia induced by prostaglandin E_2, an inflammatory mediator that acts directly to sensitize primary afferent nociceptors (Baccaglini and Hogan, 1983; Pitchford and Levine, 1991), by rolipram a type IV phosphodiesterase inhibitor. Prostaglandin E_2 plus rolipram, in the dorsum of the rat's hind paw produced a long-lasting mechanical hyperalgesia (> 3 days) and sympathectomy, done prior to injection of prostaglandin E_2 plus rolipram, prevented the prolongation of prostaglandin E_2-induced hyperalgesia by rolipram (Aley et al., 1994). In this study we further evaluated the role of sympathetic postganglionic neurons in the prolonged hyperalgesia induced by prostaglandin E_2 plus rolipram, including dependence on preganglionic sympathetic outflow and on α-adrenergic mechanisms at the site of injection of prostaglandin E_2 plus rolipram.

2. Materials and methods

Male Sprague-Dawley rats (250–300 g; Bantin and Kingman, Fremont, CA) housed in groups of two to

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three, under a 12 h light/dark cycle, were used in the experiments. Food and water were available ad libitum. Experiments were carried out under the approval of the Institutional Animal Care Commitee of the University of California, San Francisco. The rats were anesthetized with sodium pentobarbital (65 mg/kg, i.p.; Anpro Pharmaceutical, Arcadia, CA) prior to surgeries.

2.1. Behavioral testing

The nociceptive flexion reflex was quantified with a Basile Analgesymeter (Stoelting, Chicago, IL), which applies a linearly increasing mechanical force to the dorsum of the rat's hindpaw. The nociceptive threshold is defined as the force, in grams at which the rat withdraws its paw. Rats were trained during the week prior to the experiments, a procedure which produces a stable baseline threshold measurement and enhances the ability to detect the action of hyperalgesic agents (Taiwo et al., 1989). On the first day of the experiment rats were exposed to the same training procedure and the mean of the last six readings was defined as the baseline threshold. The mean baseline threshold in this group of rats were 110.29 ± 0.72 g (mean $\pm$ S.E.M; $n = 136$). Rats were exposed to the training procedure only prior to the drug treatment. Mechanical threshold (primary hyperalgesia) was determined at different time points after treatments. Three withdrawal thresholds at the site of the drug treatment were measured at 5 min intervals at each of the time points and the mean of these three values is defined as the paw withdrawal threshold at that time. The percentage change was calculated from the baseline threshold. Control rats were treated with an equivalent volume of saline.

2.2. Injection of prostaglandin E_2 plus rolipram

Prostaglandin E_2 (100 ng/2.5 μl, Sigma, St. Louis MO) was injected intradermally into the dorsum of the rats hindpaw and rolipram (1 μg/2.5 μl, Berlex Laboratory, Wayne, NJ) was injected at the same site 30 min after prostaglandin E_2. Paw-withdrawal thresholds were determined at 60, 120, 180 and 240 min and over a period of 2 weeks following injection of prostaglandin E_2.

2.3. Surgical sympathectomy

To determine the contribution of sympathetic postganglionic neurons to rolipram-induced prolongation of prostaglandin E_2 hyperalgesia, bilateral surgical sympathectomy at the L_1–L_4 paravertebral ganglion level was performed. The sympathetic chain was exposed by an extraperitoneal approach from the left side. The L_1–L_4 level of the sympathetic chain, nomenclature used as described by Baron and colleagues (Baron et al., 1988) was visualized. The L_1–L_4 paravertebral ganglia and sympathetic trunk on the left side and L_1–L_4 paravertebral ganglia and sympathetic trunk on the right side were then resected causing sympathetic denervation of the hindpaw (Baron et al., 1988). Experimental group 2 was sympathectomized 5 days prior to injection of prostaglandin E_2 plus rolipram.

2.4. Decentralization of the sympathetic postganglionic neurons

Involvement of preganglionic sympathetic neuron activity in rolipram-induced prolongation of prostaglandin E_2 hyperalgesia was examined by decentralizing the sympathetic postganglionic neuron. The lumbar sympathetic chain was visualized and the sympathetic trunk above the left L_1 ganglia as well as the white rami of the left L_1, L_2 and L_3 (when present) paravertebral ganglia were cut, decentralizing postganglionic neurons projecting to the hind paw (Baron et al., 1988). Experimental group 3 was decentralized surgically 5 days prior to injection of prostaglandin E_2 plus rolipram.

2.5. α-Adrenoceptor antagonists

To determine if an α-adrenoceptor was involved in rolipram-induced prolongation of prostaglandin E_2 hyperalgesia and to determine the site of such involvement in the mechanical hyperalgesia, intraperitoneal (i.p.), intradermal (i.d.) or intrathecal (i.t.) injections of adrenoceptor antagonists were given prior to injection of prostaglandin E_2 plus rolipram.

Phentolamine (Ciba-Geigy, Summit, NJ), an α-adrenoceptor antagonist was given 10 min prior to prostaglandin E_2, either i.p. (1 mg/kg) in experimental group 4a, or i.d. 1 μg/paw (2.5 μl) in experimental group 4b, or i.t. 10 μg/rat (10 μl) in experimental group 4c, and i.t. 25 μg/rat (10 gml) in experimental group 4d.

Prazosin (Sigma, St. Louis, MO), a relatively specific α_1-adrenoceptor antagonist was given 10 min prior to prostaglandin E_2 either i.p. 2 mg/kg in experimental group 4e, or i.d. 1 μg/paw (2.5 μl) in experimental group 4f, or i.t. 10 μg/rat (10 μl) in experimental group 4g, and i.t. 25 μg/rat (10 μl) in experimental group 4h.

Yohimbine (Sigma, St. Louis, MO), a relatively specific α_2-adrenoceptor antagonist was given 10 min prior to prostaglandin E_2 either i.p. 2 mg/kg in experimental group 4i, or i.d. 1 μg/paw (2.5 μl) in experimental group 4j, or i.t. 10 μg/rat (10 μl) in experimental group 4k, and i.t., 25 μg/rat (10 μl) in experimental group 4l.

2.6. Intrathecal catheter implantation

Two days prior to experiments, under pentobarbital anesthesia (65 mg/kg, i.p.), intrathecal (i.t.) catheters were inserted through the atlanto-occipital membrane and passed caudally 8.5 cm to a site just rostral to the lumbosacral enlargement (Yaksh and Rudy, 1976). The i.t. catheter was then anchored to the skull with bone screws and acrylic dental cement. Rats that exhibited neurological deficits, at any time following the surgical procedure, were eliminated from the study.

2.7. Drug administration

Prostaglandin E_2 (1 mg/2.5 ml, stock solution) and rolipram (10 mg/2.5 ml, stock solution) were dissolved in 10% ethanol and further dilutions were made with saline. Phentolamine and yohimbine were dissolved in saline, and prazosin was dissolved in distilled water. The selection of drug doses were based on some previous studies (Aley et al., 1994; Danzebrink and Gebhart, 1990; Howe et al., 1983; Kinnman and Levine, 1994) All the time points mentioned are in relation to the administration of prostaglandin E_2. The concentration of ethanol injected was $\leq 1\%$. Intraperitoneal and intrathecal injections of α-adrenoceptor antagonists were done 10 and 5 min prior to prostaglandin E_2, respectively. In the case of intradermal injection, the drugs were administered from the same syringe in such a way that the antagonist reached the intradermal site first.

2.8. Statistical analysis

Two way repeated measures analysis of variance (ANOVA) followed by Scheffe's post hoc test, or Mann-Whitney U test, or unpaired t test, as appropriate were used to analyze results and a P-value < 0.05 was considered statistically significant. The time course of the hyperalgesia induced by prostaglandin E_2 and that induced by prostaglandin E_2 plus rolipram are redrawn, in some figures, to aid comparisons. The results are presented as means $\pm$ S.E.M of four or more observations, and wherever error bars are not visible, they are contained within the symbol.

3. Results

3.1. Effect of prostaglandin E_2 plus rolipram

Prostaglandin E_2 (1 μg/2.5 μl) injected intradermally induced a decrease in mechanical nociceptive threshold (i.e., hyperalgesia). The paw-withdrawal thresholds remained decreased for about 120 min and returned to baseline by 240 min. Rolipram (1 μg/2.5 μl), injected 30 min after prostaglandin E_2 prolonged the hyperalgesia induced by prostaglandin E_2. The prolongation of the prostaglandin E_2-induced hyperalgesia by rolipram remained below that of the vehicle control group for > 3 days (Fig. 1A, B). Two factor repeated measures of ANOVA showed a significant difference in the paw-withdrawal thresholds in response to rolipram ($P < 0.05$). Subsequent analysis with Mann-Whitney U-test, unpaired t-test, and Scheffe's post-hoc test revealed that rolipram-induced prolongation of prostaglandin E_2 hyperalgesia was statistically significant ($P < 0.05$). Rolipram alone had no significant effect on mechanical paw withdrawal threshold (data not shown).

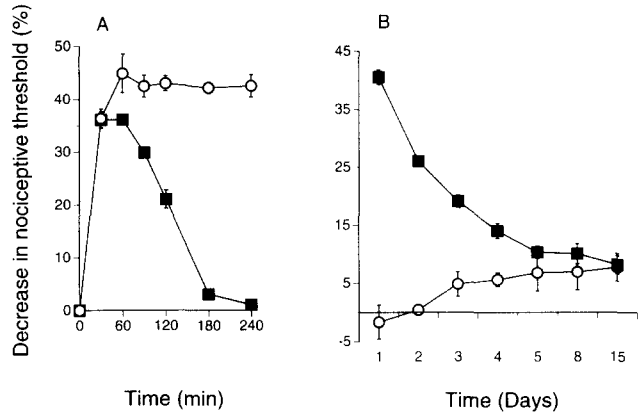

Fig. 1. (A) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 60, 120, 180, and 240 min after intradermal (i.d.) injection of prostaglandin E_2 alone (■, $n = 12$) or when rolipram (a type IV phophodiesterase inhibitor, 1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$). (B) The effect of prostaglandin (E_2 (100 ng) plus rolipram (1 μg) on mechanical nociceptive thresholds on days 1 (1 hr after injection), 2, 3, 4, 5, 8, and 15 (■ $n = 6$) after the injection or the effect of saline on mechanical nociceptive thresholds on days 1 (1 h after injection), 2, 3, 4, 5, 8, and 15 (○, $n = 6$) after the injection.

3.2. Effect of surgical sympathectomy

Surgical lumbar sympathectomy (L_1–L_4) done prior to injection of prostaglandin E_2 plus rolipram attenuated rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. ANOVA followed by Scheffe's post-hoc test revealed that rolipram-induced prolongation of prostaglandin E_2 hyperalgesia was significantly attenuated by prior sympathectomy (Fig. 2B, $P < 0.05$).

3.3. Role of preganglionic sympathetic outflow

Decentralization of the lumbar sympathetic chain done prior to injection of prostaglandin E_2 plus rolipram, did not significantly affect the rolipram-induced prolongation of prostaglandin E_2 hyperalgesia (ANOVA, followed by Scheffe's post-hoc test, Fig. 3B,

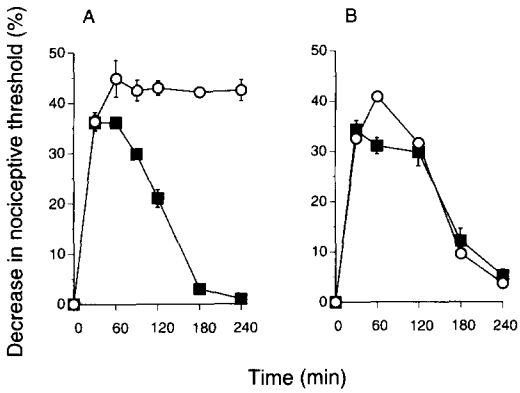

Fig. 2. (A) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 30, 60, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$), in normal rats. (B) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold at 30, 60, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 6$), $P < 0.05$) in sympathectomized rats.

$P > 0.05$,). Rolipram-induced prolongation of prostaglandin E_2-induced hyperalgesia in decentralized (lumbar sympathetic chain) rats was similar to that in normal rats (Fig. 3B).

3.4. Role of adrenoceptors

3.4.1. Phentolamine

Systemic (i.p.) and intradermal injections of phentolamine, when given prior to prostaglandin E_2 plus rolipram significantly attenuated rolipram-induced pro-

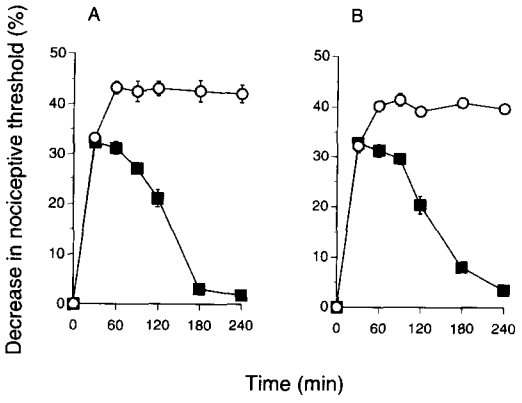

Fig. 3. (A) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 30, 60, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$), in normal rats. (B) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold at 30, 60, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 6$, $P > 0.05$) in rats in which SPGNs were decentralized.

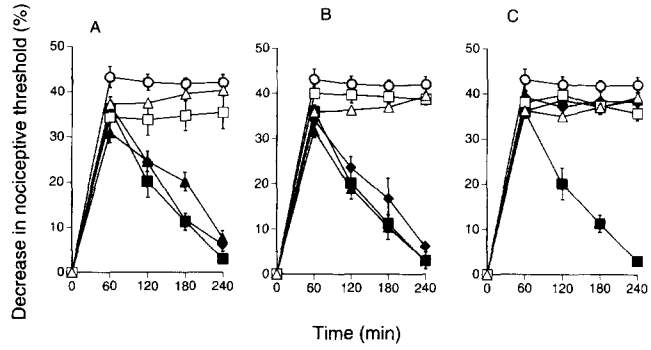

Fig. 4. (A) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 60, 90, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$), or when rats were pretreated with phentolamine i.p. (α-adrenoceptor antagonist, 1 mg/kg, ▲, $n = 6$, $P < 0.05$) or when rats were pretreated with phentolamine 1 μg/paw, i.d. (◆, $n = 6$, $P < 0.05$), or when rats were pretreated with phentolamine 10 μg/rat i.t. (□, $n = 4$, $P > 0.05$), and when rats were pretreated with phentolamine 25 μg/rat i.t. (△, $n = 4$, $P > 0.05$). (B) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 60, 90, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$), or when rats were pretreated with prazosin i.p. (α_1-adrenoceptor antagonist, 2 mg/kg, ▲, $n = 6$, $P < 0.05$) or when rats were pretreated with prazosin 1 μg/paw, i.d. (◆, $n = 6$, $P < 0.05$), or when rats were pretreated with prazosin 10 μg/rat i.t. (□, $n = 4$, $P > 0.05$), and when rats were pretreated with prazosin 25 μg/rat i.t. (△, $n = 4$, $P > 0.05$). (C) The effect of prostaglandin E_2 (100 ng) on mechanical nociceptive threshold 60, 90, 120, 180, and 240 min after i.d. injection of prostaglandin E_2 alone (■), or when rolipram (1 μg) was injected 30 min after prostaglandin E_2 (○, $n = 12$), or when rats were pretreated with yohimbine i.p. (α_2-adrenoceptor antagonist, 2 mg/kg, ▲, $n = 6$, $P > 0.05$) or when rats were pretreated with yohimbine 1 μg/paw, i.d. (◆, $n = 6$, $P > 0.05$), or when rats were pretreated with yohimbine 10 μg/rat i.t. (□, $n = 6$, $P > 0.05$), and when rats were pretreated with yohimbine 25 μg/rat i.t. (△, $n = 6$, $P > 0.05$).

longation of prostaglandin E_2 hyperalgesia as analyzed by ANOVA, and Scheffe's post-hoc test (Fig. 4A, $P < 0.05$). Intrathecal injections of phentolamine (10 μg and 25 μg/rat) did not alter the rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. (ANOVA followed by Scheffe's post-hoc test Fig. 4A, $P > 0.05$). Phentolamine (doses employed in this study) alone had no significant effect on paw withdrawal threshold (data not shown).

3.4.2. Prazosin

Systemic and intradermal injections of prazosin, when given prior to prostaglandin E_2 plus rolipram significantly attenuated rolipram-induced prolongation of prostaglandin E_2 hyperalgesia (ANOVA, followed by Scheffe's post-hoc test, Fig. 4B, $P < 0.05$). Intrathecal injection of prazosin (10 μg and 25 μg/rat) was without significant effect on rolipram-induced prolongation of prostaglandin E_2 hyperalgesia (ANOVA, and Scheffe's post-hoc test, Fig. 4B, $P > 0.05$). Prazosin

(doses employed in this study) alone had no significant effect on paw-withdrawal threshold (data not shown).

3.4.3. Yohimbine

Whether given systemically (i.p.), intradermally or intrathecally (10 μg and 25 μg/rat) was without significant effect on rolipram-induced prolongation of prostaglandin E_2 hyperalgesia (ANOVA, followed by Scheffe's post-hoc test, Fig. 4C, all $P > 0.05$,). Yohimbine (doses employed in this study) alone had no significant effect on paw-withdrawal threshold (data not shown).

4. Discussion

A contribution of sympathetic postganglionic neurons to sensitization of small-diameter afferents (Xie and Xiao, 1990) and to mechanical hyperalgesia (Aley et al., 1994; Kim and Chung, 1991; Kinnman and Levine, 1994; Levine et al., 1986; Neil et al., 1991; Shir and Seltzer, 1991) has been suggested by a number of previous studies with neuropathic pain models. The present study confirms that the sympathetic postganglionic neuron also contributes to a prolonged mechanical hyperalgesia induced by prostaglandin E_2 plus rolipram (Aley et al., 1994). The effects of α-adrenoceptor antagonists indicate that α_1-adrenoceptors are involved in this sympathetically maintained mechanical hyperalgesia, since phentolamine and prazosin both blocked rolipram-induced prolongation of prostaglandin E_2-hyperalgesia when given intraperitoneally 10 min prior to prostaglandin E_2 plus rolipram. This result is consistent with the recently observed block of capsaicin-induced sympathetically-dependent secondary hyperalgesia by prazosin in rats (Kinnman and Levine, 1994), and with studies of patients with neuropathic pain (Davis et al., 1991), in whom topical application of an α_2-adrenoceptor agonist (clonidine) relieved sympathetically maintained pain, while injection of an α_1-adrenoceptor specific agonist (phenylephrine) at the site of topically-applied clonidine evoked intense pain. The intradermal injection of the α-adrenoceptor antagonists (phentolamine and prazosin), injected at the site at which prostaglandin E_2 plus rolipram were subsequently injected, blocked the rolipram-induced prolongation of prostaglandin E_2 hyperalgesia, while intrathecal administration of these agents did not. Though the intrathecal administration of phentolamine did not block the rolipram-induced prolongation of prostaglandin E_2 hyperalgesia, it did not block the enhancement of its amplitude (Fig. 4A), which may be due to the effect of phentolamine on the central nervous system. Yohimbine, an α_2-adrenoceptor antagonist failed to inhibit rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Thus, the sympathetic postganglionic neuron is proposed to interact with sensory afferents via an α_1-adrenoceptor mechanism in the skin to cause primary afferent sensitization and mechanical hyperalgesia. The effects of phentolamine and prazosin were temporary as the paw-withdrawal thresholds of these groups of rats (phentolamine/prostaglandin E_2/rolipram- or prazosin/prostaglandin E_2/rolipram-treated) were found to be lower than their baseline thresholds on the day following injection of phentolamine (unpublished observations), suggesting that prostaglandin E_2 plus rolipram induces sustained changes in the way the sympathetic postganglionic neuron interacts with sensory afferents.

While the sympathetically maintained hyperalgesia observed in the present study was dependent on an α_1-adrenoceptor mechanism, we (Gold et al., 1994; Levine et al., 1986) and others (Sato and Perl, 1991) have implicated an α_2-adrenoceptor involvement in other animal models of sympathetically maintained pain. One difference between the model used in the present study and those used in previous studies involving α_2-adrenoceptor mechanisms is that previous models involved either overt nerve injury (Sato and Perl, 1991), or use of a pharmacological agent to mimic nerve injury (i.e., chloroform or the calcium ionophore, A23187 (Gold et al., 1994; Levine et al., 1986; Taiwo et al., 1990)). In the above mentioned experiments, norepinephrine-induced hyperalgesia in the chloroform treated rats is prevented by indomethacin and attenuated by sympathectomy, and hence we have suggested that an interaction of the catecholamines with the receptors on sympathetic postganglionic neuron terminals release prostaglandins, which in turn mediate the hyperalgesic effect (Levine et al., 1986) and the α_2-adrenoceptor contributing to sympathetically maintained pain is located presynaptically on the sympathetic postganglionic neuron terminal in the skin (Gold et al., 1994; Levine et al., 1986). Since prostaglandin E_2 is known to act directly on primary afferent nociceptors to sensitize them (Baccaglini and Hogan, 1983; Pitchford and Levine, 1991) and rolipram, alone, had no effect on mechanical nociceptive threshold in the skin, and since α_1-adrenoceptors are more often post- rather than pre-synaptic (Langer, 1974; Weiner, 1985), we suggest that in the present model of sympathetically dependent pain the α_1-adrenoceptor is located on the primary afferent nociceptor. Decentralization of the lumbar sympathetic chain did not alter rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Thus, the contribution of the sympathetic postganglionic neuron to the sympathetically dependent hyperalgesia is independent of activity in preganglionic sympathetic neurons. By what mechanism rolipram induces an interaction between the sympathetic postganlionic neuron and primary afferent terminals in the skin mediating this sympathetically dependent hyperalgesia remain to be explored.

In conclusion, we provide evidence to suggest that sympathetic postganglionic neurons and α-adrenoceptors are involved in rolipram-induced prolongation of prostaglandin E_2 hyperalgesia. Furthermore, we propose that the sympathetic postganglionic neuron interaction with sensory afferents, which is via an α_1-adrenoceptor mechanism in the skin, to cause prolonged mechanical hyperalgesia, is independent of activity in preganglionic sympathetic neurons.

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